

REMARKS

Claims 136-155 are pending in the subject application. Claims 136 and 142 have been amended and claims 153 and 154 have been cancelled. Accordingly, upon entry of this Amendment, claims 136-152 and 155 will be pending and under examination.

In making these amendments, applicants neither concede the correctness of the Examiner's rejections in the November 4, 2004 Office Action, nor abandon the right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application.

Support for the term "unconcentrated" recited in amended claims 136 and 142 may be found, *inter alia*, in the specification at page 47, lines 33 and 34. Applicants maintain that the amendments to the claims do not raise any issue of new matter, and that these claims are fully supported by the specification as originally filed. Accordingly, applicants respectfully request that this Amendment be entered.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the November 4, 2004 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods of diagnosing a thyroid condition in a subject. One method, that of claims 136-

141 and 155 (as dependent thereon) comprises obtaining a suitable unconcentrated urine sample from the subject, and determining a concentration of thyroid stimulating hormone (TSH) in the sample by a method which is not a radioimmunoassay, wherein (i) a concentration of TSH greater than about 0.35 μ IU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, diagnoses hypothyroidism in the subject, and (ii) a concentration of TSH less than about 0.04 μ IU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, diagnoses hyperthyroidism in the subject.

Another method, that of claims 142-152 and 155 (as dependent thereon), comprises obtaining a suitable unconcentrated urine sample from the subject, and determining a concentration of TSH and a concentration of thyroxine in the sample by a method which is not a radioimmunoassay, wherein (i) a concentration of TSH greater than about 0.35 μ IU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, and a concentration of thyroxine greater than about 1.5 ng/ml in the subject's urine diagnoses hypothyroidism in the subject, and (ii) a concentration of TSH less than about 0.04 μ IU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, and a concentration of thyroxine less than about 0.3 ng/ml in the subject's urine diagnoses hyperthyroidism in the subject.

This invention is based on applicants' surprising discovery that measuring the concentration of either (1)

urinary TSH or (2) urinary TSH and urinary thyroxine can reliably detect hypothyroidism and hyperthyroidism. In addition, this invention is characterized by the use of a urine sample which is *unconcentrated*.

Rejection Under 35 U.S.C. §103(a) - Obviousness

The Examiner rejected claims 136-141 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuku, et al. (Journal of Endocrinology, 1974, Vol. 62, pages 645-655), in view of Schuurs, et al. (U.S. Patent No. 4,016,043).

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In response to the Examiner's rejection, applicants respectfully traverse. Applicants maintain that the Examiner has failed to make a prima facie case of obviousness.

The claimed invention is discussed above.

For prima facie obviousness to exist, the cited references in combination must (i) teach all elements of the claimed invention, (ii) create a motive to combine, and (iii) create a reasonable expectation of success. The cited references fail to do this.

Specifically, the references, when combined, do not teach all elements of the claimed method. For example, neither reference teaches the element of an *unconcentrated urine sample* recited in the claims, as amended. The Examiner asserts that using unconcentrated urine would be an obvious variation as purification steps would thereby be eliminated. However, applicants maintain that the Examiner's assertion is based on hindsight, and does not

factor in applicants' surprising discovery that measuring the concentration of either (1) urinary TSH or (2) urinary TSH and urinary thyroxine can reliably detect hypothyroidism and hyperthyroidism.

Thus, Kuku, et al. and Schuus, et al., in combination, fail to teach or suggest all elements of the claimed invention. It follows that these references also fail to provide a motive to combine as a reasonable expectation of success.

Furthermore, applicants traverse the Examiner's position that Kuku et al. teach the TSH concentration ranges of the claims, and maintain as flawed the Examiner's method of comparing the claimed invention with the teachings of Kuku, et al. In short, the claimed invention comprises measuring the *concentration* of TSH, i.e., the amount of TSH per unit volume of fluid at a single time point. Kuku et al., in contrast, teach measuring the *rate* of urinary excretion of TSH, i.e., the amount of TSH secreted per unit of time. These two notions are entirely distinct, despite certain quantitative relationships between them which might exist under certain circumstances. To equate them as the Examiner has done is flawed, as is evident from the Examiner's incorrect calculations (e.g., $(10.8\mu\text{u/hr})(12\text{h}) = 129.6\mu\text{u/ml}$).

The Examiner also rejected claims 142-155 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuku et al., in view of Schuurs, et al. and Philo, et al. (U.S. Patent No. 5,108,896).

In response to the rejection of claims 153 and 154, applicants note that these claims have been cancelled, rendering the rejection thereof moot.

In response to the rejection of the remaining claims, applicants respectfully traverse.

The claimed invention is discussed above, as is the standard for a prima facie case of obviousness.

Kuku et al. and Schuurs, et al. combined fail to teach all elements of the method of claims 142-152 and 155, for the reasons set forth above regarding claims 136-141. Philo, et al., combined with these two references, fails to cure their shortcomings, in that Philo, et al. fail to teach or suggest (i) the element of an unconcentrated urine sample recited in the claims, as amended, or (ii) applicants' surprising finding that measuring the concentration of either (1) urinary TSH or (2) urinary TSH and urinary thyroxine can reliably detect hypothyroidism and hyperthyroidism. Instead, Philo, et al. provide a general teaching of simultaneous immunoassays of two analytes using dual enzyme-labeled antibodies.

Thus, Kuku, et al., Schuurs, et al. and Philo, et al., in combination, fail to teach or suggest all elements of the

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claimed invention. It follows that these references also fail to provide a motive to combine or a reasonable expectation of success.

In view of the above, applicants maintain that claims 136-152 and 155 satisfy the requirements of 35 U.S.C. §103.

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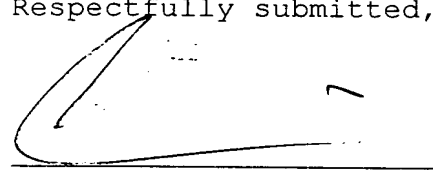
Summary

Applicants maintain that claims 136-152 and 155 are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed \$510.00 extension fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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5/7/05
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